Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Paraneoplastic neurological syndromes.

Bibliographic Source(s)

Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Honnorat J, Sillevis Smitt PA, Verschuuren JJ, Voltz R, Paraneoplastic Neurological Syndrome Euronetwork. Paraneoplastic neurological syndromes. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 447-57. [92 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevis Smitt PA, Verschuuren JJ, Voltz R, Paraneoplastic Neurological Syndrome Euronetwork. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):682-90.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Points [GPP]) are defined at the end of the "Major Recommendations" field.

Recommendations (GPP)

- Patients with paraneoplastic neurological syndrome (PNS) most often present with neurological symptoms before an underlying tumour is detected. Onconeural antibodies should be sought in sera from patients with suspected PNS. The antibodies are important for diagnosis and tumour search.
- Radiological investigations for tumours, such as high resolution computed tomography (CT) for the detection of small cell lung cancer (SCLC), are important, but should be followed by fluorodeoxyglucose positron-emission tomography (FDG-PET) if no tumour is found.
- Patients should also be followed at regular intervals, for example every 6 months for up to 4 years, to search for tumour in cases where the initial tumour screen was negative.
- Early detection and treatment of the tumour is the approach that offers the greatest chance for PNS stabilization. This should be done in cooperation with the oncologist, pulmonologist, gynaecologist or paediatrician depending on the associated tumour.
- Immune therapy (steroids, plasma exchange, or intravenous immunoglobulin) usually has no or modest effect on paraneoplastic limbic encephalitis (PLE), subacute sensory neuropathy (SSN) or paraneoplastic cerebellar degeneration (PCD).

- Children with paraneoplastic opsoclonus-myoclonus (POM) may respond to immune therapy, whereas no clear evidence of such therapy has been shown in adults with POM.
- Patients with Lambert-Eaton myasthenic syndrome (LEMS) or paraneoplastic peripheral nerve hyperexcitability (PPNH) should be treated with immune therapy if symptomatic therapy does not give sufficient improvement.
- Symptomatic therapy should be offered to all patients with PNS.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point Where there was lack of evidence but consensus was clear the task force members have stated their opinion as Good Practice Points.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Paraneoplastic neurological syndromes (PNS):

- Limbic encephalitis
- Subacute sensory neuronopathy
- Cerebellar degeneration
- Opsoclonus-myoclonus
- Lambert–Eaton myasthenic syndrome
- Peripheral nerve hyperexcitability

Note: Myasthenia gravis, paraproteinemic neuropathies, paraneoplastic retinopathy and dermatomyositis have not been included in this report.

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Oncology

Pediatrics

Intended Users

Physicians

Guideline Objective(s)

To outline guidelines for the management of classical paraneoplastic neurological syndromes (PNS)

Target Population

Patients with paraneoplastic neurological syndromes (PNS)

Interventions and Practices Considered

Diagnosis/Evaluation

1. Assessment of onconeuronal antibodies
2. High-resolution computed tomography (CT) and fluorodeoxyglucose positron-emission tomography (FDG-PET)
3. Follow-up at regular intervals to search for tumors

Management/Treatment

1. Treatment of underlying tumor
2. Specialist consultation
3. Immune therapy (steroids, plasma exchange, or intravenous immunoglobulin) for children with paraneoplastic opsoclonus myoclonus (POM) or adults with Lambert–Eaton myasthenic syndrome (LEMS) or peripheral nerve hyperexcitability (PPNH)
4. Symptomatic therapy

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Effectiveness of treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Search strategies have included English literature from the following databases: Cochrane Library, MedLine, PubMed (last search August 2009). The key words used for the search included 'limbic encephalitis', 'sensory neuronopathy' 'cerebellar ataxia', 'opsoclonus-myoclonus', 'Lambert–Eaton myasthenic syndrome', 'neuromyotonia' in combination with 'investigation' and 'therapy'.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test

is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

All evidence available was evaluated as Class IV – case reports, case series and expert opinion (see the "Rating Scheme for the Strength of the Evidence" field). Thus no recommendations reach Level A, B or C. Good Practice Points were agreed by consensus (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point Where there was lack of evidence but consensus was clear the task force members have stated their opinion as Good Practice Points.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

All evidence available was evaluated as Class IV – case reports, case series, and expert opinion. Thus, no recommendations reach Level A, B, or C . However, Good Practice Points (GPP) were agreed by consensus (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of paraneoplastic neurological syndromes (PNS)

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Jul (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

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Guideline Committee

European Federation of Neurological Societies Task Force on Paraneoplastic Neurological Syndromes

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The authors have reported no conflicts of interest relevant to this manuscript.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on April 6, 2007. The information was verified by the guideline developer on May 15, 2007. This NGC summary was updated by ECRI Institute on February 20, 2012.

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